

Claims

1. A composition comprising a decoy peptide which binds to a neurotoxic  $\beta$ -amyloid peptide and reduces the ability of the neurotoxic  $\beta$ -amyloid peptide to form aggregates which increase calcium influx into neuronal cells.

2. The composition of claim 1 wherein the decoy peptide is non-hydrolyzable.

3. The composition of claim 2 wherein the decoy peptide is selected from the group consisting of peptides comprising D-amino acids, peptides comprising a  $-\text{psi}[\text{CH}_2\text{NH}]$ - reduced amide peptide bond, peptides comprising a  $-\text{psi}[\text{COCH}_2]$ - ketomethylene peptide bond, peptides comprising a  $-\text{psi}[\text{CH}(\text{CN})\text{NH}]$ - (cyanomethylene)amino peptide bond, peptides comprising a  $-\text{psi}[\text{CH}_2\text{CH}(\text{OH})]$ - hydroxyethylene peptide bond, peptides comprising a  $-\text{psi}[\text{CH}_2\text{O}]$ - peptide bond, and peptides comprising a  $-\text{psi}[\text{CH}_2\text{S}]$ - thiomethylene peptide bond.

4. The composition of claim 1 wherein the neurotoxic  $\beta$ -amyloid peptide is selected from the group consisting of  $\beta\text{AP}_{1-42}$  and  $\beta\text{AP}_{25-35}$ .

5. The composition of claim 1 wherein the decoy peptide has  $\beta$  sheet forming potential.

6. The composition of claim 5 wherein the decoy peptide is between 4 and 20 amino acids in length.

7. The composition of claim 6 wherein the decoy peptide is between 5 and 10 amino acids in length.

8. The composition of claim 5 wherein the decoy peptide is a cyclized peptide.

9. The composition of claim 4 wherein the decoy peptide comprises a sequence selected from the group consisting of amino acids 1-6 of SEQ ID NO:1, amino acids 1-6 of SEQ ID

NO:2, amino acids 1-6 of SEQ ID NO:3, amino acids 1-6 of SEQ ID NO:4, amino acids 1-6 of SEQ ID NO:5, amino acids 1-6 of SEQ ID NO:6, amino acids 1-6 of SEQ ID NO:7, amino acids 1-6 of SEQ ID NO:8, amino acids 1-9 of SEQ ID NO:9, amino acids 1-7 of SEQ ID NO:12, amino acids 1-7 of SEQ ID NO:13, amino acids 1-7 of SEQ ID NO:14, amino acids 1-6 of SEQ ID NO:15, amino acids 1-5 of SEQ ID NO:16, amino acids 1-9 of SEQ ID NO:17, amino acids 1-9 of SEQ ID NO:18, amino acids 1-7 of SEQ ID NO:19, amino acids 1-5 of SEQ ID NO:21, amino acids 1-5 of SEQ ID NO:22, amino acids 1-5 of SEQ ID NO:23, amino acids 1-5 of SEQ ID NO:24, amino acids 1-5 of SEQ ID NO:25, amino acids 1-5 of SEQ ID NO:26, amino acids 1-5 of SEQ ID NO:27, amino acids 1-6 of SEQ ID NO:28, amino acids 1-6 of SEQ ID NO:29, and amino acids 1-6 of SEQ ID NO:30.

10. The composition of claim 9 wherein the decoy peptide comprises a sequence selected from the group consisting of amino acids 1-6 of SEQ ID NO:2, amino acids 1-6 of SEQ ID NO:9 and amino acids 1-9 of SEQ ID NO:17.

11. The composition of claim 1 wherein the decoy peptide is conjugated to a compound which facilitates transport across the blood-brain barrier into the brain.

12. The composition of claim 11 wherein the compound is selected from the group consisting of a transferrin receptor binding antibody, cationized albumin, Met-enkephalin, lipoidal forms of dihydropyridine, cationized antibodies, and docosohexanoic acid.

13. The composition of claim 1 wherein the neuronal cells are NT2-N cells differentiated with retinoic acid.

14. A method for treating a subject having a condition characterized by neurotoxic  $\beta$ -amyloid peptide aggregates comprising administering to the subject an amount of a decoy peptide which binds to a neurotoxic  $\beta$ -amyloid peptide and reduces the ability of the neurotoxic  $\beta$ -amyloid peptide to form aggregates which increase calcium influx into neuronal cells effective to reduce neurotoxic  $\beta$ -amyloid peptide aggregate formation in the subject.

24. A pharmaceutical composition comprising an amount of a decoy peptide which binds to a neurotoxic  $\beta$ -amyloid peptide and reduces the ability of the neurotoxic  $\beta$ -amyloid peptide to form aggregates which increase calcium influx into neuronal cells effective to reduce neurotoxic  $\beta$ -amyloid peptide aggregate formation, and a pharmaceutically acceptable carrier.

25. The pharmaceutical composition of claim 24, wherein the decoy peptide is conjugated to a compound which facilitates transport across the blood-brain barrier into the brain.

5 26. A pharmaceutical composition comprising an amount of a non-NMDA channel antagonist effective to reduce neuronal cell calcium influx, and a pharmaceutically acceptable carrier.

10 27. The pharmaceutical composition of claim 26, wherein the non-NMDA channel antagonist is selected from the group consisting of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), 6,7-dinitroquinoxaline-2,3(1H, 4H)-dione (DNQX), 2,3-dihydroxy-nitro-7-sulfamoyl-benzo[f]quinoxaline (NBQX), 1-(4-chlorobenzoyl)piperazine-2,3-dicarboxylic acid (CBPD), 6,7-dichloro-2(1H)-oxoquinoline-3-phosphonic acid (24c), Evans blue, 2,3-dihydroxy-7-sulfamoyl-benzo[f]quinoxaline (BQX), derivatives of 4-oxo-1,4-dihydroquinoline-2-carboxylic acid at the 6-position, 2-amino-3-[3-(carboxymethoxy)-5-methylisoxazol-4-yl]propionic acid (AMOA), 2-amino-3-[2-(3-hydroxy-5-methylisoxazol-4-yl)-methyl-5-methyl-3-oxoisoxazolin-4-yl]propionic acid (AMNH), 1-(4-amino-phenyl)-4-methyl-7,8-methyl-endioxyl-5H-2,3-benzodiazepine (GYKI 52466), 6-(1H-imidazol-1-yl)-7-nitro- 2,3(1H,4H)-quinoxalinedione hydrochloride (YM90K), 1-(4-aminophenyl)- 3-methylcarbamy-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (GYKI 53655), and (-)(3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid monohydrate (LY326325).

25 28. The pharmaceutical composition of claim 24 or 26, further comprising a compound which increases transport across the blood-brain barrier.

30 29. A method for identifying lead compounds for a pharmacological agent useful in the treatment of conditions associated with  $\beta$ -amyloid peptide ( $A\beta$ ) aggregation, comprising forming a mixture comprising a  $A\beta$  peptide containing a  $\beta$ -sheet forming domain, a decoy peptide which binds to a neurotoxic  $\beta$ -amyloid peptide, and a candidate

incubating the mixture under conditions which, in the absence of the candidate pharmacological agent, permit the decoy peptide to selectively bind the neurotoxic  $\beta$ -amyloid peptide containing a  $\beta$ -sheet forming domain, and

30. The method of claim 29 wherein the candidate pharmacological agent is a peptide.

32. A method for identifying lead compounds for a pharmacological agent useful in the treatment of conditions associated with increased neuronal cell calcium influx induced by the presence of  $\beta$ -amyloid peptide (A $\beta$ ) aggregates, comprising

forming a mixture comprising a A $\beta$  containing a  $\beta$ -sheet forming domain, and a candidate pharmacological agent,

incubating the mixture under conditions which, in the absence of the candidate pharmacological agent, permit the A $\beta$  to aggregate,

contacting the neuronal cell with the mixture, under conditions which, in the presence of A $\beta$  aggregates, permit influx of calcium into the neuronal cell, and

detecting the calcium-sensitive compound as a measure of the relative presence of calcium in the neuronal cell, wherein detection of a lesser amount of calcium in the neuronal cell than is present when the neuronal cell is contacted with A $\beta$  aggregates indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which disrupts A $\beta$  aggregation.

33. The method of claim 32 wherein the candidate pharmacological agent is a peptide.

34. The method of claim 32 wherein the candidate pharmacological agent is a non-NMDA channel antagonist.

35. The method of claim 32 wherein the candidate pharmacological agent is a small organic molecule.

36. A method for identifying lead compounds for a pharmacological agent useful in the treatment of conditions associated with increased neuronal cell calcium influx induced by the presence of  $\beta$ -amyloid peptide ( $A\beta$ ) aggregates, comprising  
providing a neuronal cell loaded with a calcium-sensitive compound which is detectable in the presence of calcium,  
contacting the neuronal cell with  $A\beta$  aggregates under conditions which permit calcium influx into the neuronal cell,  
detecting the calcium-sensitive compound as a measure of calcium influx induced by  $A\beta$  aggregates,  
contacting the neuronal cell with a candidate pharmacological agent, and  
detecting the calcium-sensitive compound as a measure of the relative presence of calcium in the neuronal cell induced by the candidate pharmacological agent, wherein detection of a lesser amount of calcium in the neuronal cell than is present when the neuronal cell is contacted with  $A\beta$  aggregates indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which reduces  $A\beta$  aggregate induced neuronal cell calcium influx.

37. The method of claim 36 wherein the candidate pharmacological agent is a peptide.

38. The method of claim 36 wherein the candidate pharmacological agent is a non-NMDA channel antagonist.

39. The method of claim 36 wherein the candidate pharmacological agent is a small

organic molecule.

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40. A method for identifying lead compounds for a pharmacological agent useful in the treatment of conditions associated with increased neuronal depolarization induced by the presence of  $\beta$ -amyloid peptide ( $A\beta$ ) aggregates, comprising  
5 providing a neuronal cell in a medium containing a potentiometric compound, wherein the influx into the neuronal cell of the potentiometric compound upon depolarization of the neuronal cell is detectable,  
forming a mixture comprising a  $A\beta$  containing a  $\beta$ -sheet forming domain, and a  
10 candidate pharmacological agent,  
incubating the mixture under conditions which, in the absence of the candidate pharmacological agent, permit the  $A\beta$  to aggregate,  
contacting the neuronal cell with the mixture, under conditions which, in the presence of  $A\beta$  aggregates, permit influx of a control amount of the potentiometric compound into the  
15 neuronal cell, and  
detecting the potentiometric compound as a measure of the relative depolarization of the neuronal cell, wherein detection of a lesser amount of potentiometric compound in the neuronal cell than is present when the neuronal cell is contacted with  $A\beta$  aggregates indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent  
20 which disrupts  $A\beta$  aggregation.

41. The method of claim 40 wherein the candidate pharmacological agent is a peptide.

42. The method of claim 40 wherein the candidate pharmacological agent is a small  
25 organic molecule.

43. The method of claim 40, wherein the potentiometric compound is fluorescent.

44. The method of claim 43, wherein the potentiometric compound is bis-(1,3-dibutylbarbituric acid)trimethine oxonol ( $DiBAC_4(3)$ ).  
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45 A method for identifying lead compounds for a pharmacological agent useful in the treatment of conditions associated with increased neuronal depolarization induced by the presence of  $\beta$ -amyloid peptide ( $A\beta$ ) aggregates, comprising

providing a neuronal cell in a medium containing a potentiometric compound,

5 wherein the influx into the neuronal cell of the potentiometric compound upon depolarization of the neuronal cell is detectable,

contacting the neuronal cell with  $A\beta$  aggregates under conditions which permit influx of a control amount of the potentiometric compound into the neuronal cell,

detecting the potentiometric compound in the neuronal cell as a measure of

10 depolarization induced by  $A\beta$  aggregates,

contacting the neuronal cell with a candidate pharmacological agent, and

detecting the potentiometric compound in the neuronal cell as a measure of the relative depolarization of the neuronal cell in the presence of the candidate pharmacological agent, wherein detection of a lesser amount of potentiometric compound in the neuronal cell  
15 than is present when the neuronal cell is contacted with  $A\beta$  aggregates but not the candidate pharmacological agent indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which reduces  $A\beta$  aggregate induced neuronal cell depolarization.

20 46. The method of claim 45 wherein the candidate pharmacological agent is a peptide.

47. The method of claim 45 wherein the candidate pharmacological agent is a small organic molecule.

25 48. The method of claim 45, wherein the potentiometric compound is fluorescent.

49. The method of claim 48, wherein the potentiometric compound is bis-(1,3-dibutylbarbituric acid)trimethine oxonol ( $DiBAC_4(3)$ ).

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